Q J NUCL MED MOL IMAGING 2015;59:359-73

Early detection of prostate cancer relapse by biochemistry and diagnostic imaging

L. EVANGELISTA [1], F. ZATTONI [2], E. ROSSI [3], R. J. KARNES [4], V. LOWE [5]

[1]Radiotherapy and Nuclear Medicine Unit
Veneto Institute of Oncology IOV – IRCCS, Padua, Italy
[2]Department of Surgical,
Oncological and Gastroenterological Sciences-Urology
University of Padua, Padua, Italy
[3]Department of Surgery, Oncology and Gastroenterology
Oncology Section, University of Padua, Padua, Italy
[4]Department of Urology, Mayo Clinic, Rochester, MN, USA
[5]Division of Nuclear Medicine
Mayo Clinic, Rochester, MN, USA

Prostate cancer (PCa) is a common malignancy in men associated with an increase in the incidence rate. Radical prostatectomy (RP) or external beam radiotherapy (EBRT) represents the most employed treatments for the local control of disease. However, 10-50% of patients who experienced a recurrence of disease after primary treatments can benefit from salvage or palliative therapies. To date, prostate specific antigen (PSA) is usually used in clinical practice to monitor the status of disease and to early detect the recurrence of PCa. Nevertheless, PSA cannot discriminate the presence of local vs. distant metastatic disease. Circulating tumor cells are considered as a sign of disease widespread, but their correlation with metastatic PCa and local recurrence of disease is still indeterminate. Digital rectal exploration and transrectal ultrasonography are considered the first clinical and diagnostic approach to identify the local recurrence of PCa, but are associated with a low detection rate and low diagnostic accuracies. Conversely, magnetic resonance imaging (MRI) has gained a great importance in this setting of disease, being able to determine the presence of local recurrence with high sensitivity, also in the presence of low serum PSA levels. Lastly, the introduction of positron emission tomography/computed tomography (PET/CT) with radiolabeled choline agents let to improve the management of patients with early recurrence of disease, although its accuracy is linked to the PSA and PSA dynamic values. New radiopharmaceutical agents, like 68Ga-PSMA or 18F-FACBC and others could improve the diagnostic accuracy of PET/CT, but the data is still preliminary. In the present review we will discuss both clinical and diagnostic instrumentations, actually available in clinical practice, able to early identify the presence of recurrent PCa and to differentiate between local and distant relapse of tumor.

KEY WORDS: Prostatic neoplasms - Prostate-specific antigen - Neoplastic cells, circulating - Ultrasonography - Magnetic resonance imaging - Positron-emission tomography - Tomography, X-ray computed.

Corresponding author: L. Evangelista, Radiotherapy and Nuclear Medicine Unit, Veneto Institute of Oncology IOV – IRCCS, Via Gattamelata 64, 35128 Padua, Italy. E-mail: laura.evangelista@ioveneto.it

Prostate cancer (PCa) is a common malignancy in men and its incidence continues to rise in many countries.[1] For its relevance, a lot of effort is poses in the detection of individuals who would most benefit from early screening, reducing over diagnosis and overtreatment while maintaining the benefits (*i.e.* lower mortality). The use of prostate-specific antigen (PSA) as a screening test has been used since the 1980s and it revolutionized PCa diagnosis.[2] It is the most effective organ (but not cancer) specific biomarker currently available for the PCa screening. Its role is essential not only in the every phase of the diagnosis but also defining the probability of disease control after definitive treatment, and indicating patients' response to treatment. Bio-

chemical PCa relapse after definitive local therapy is a tricky aspect of PSA monitoring since the sole manifestation of disease recurrence could be a detectable and increasing PSA value. PSA-only recurrence faces a difficult set of decisions since several aspects have to be taken into considerations: 1) to delay the onset of metastatic disease and death; 2) to avoiding overtreating patients whose disease; and 3) to face the patients' anxiety of a tumor recurrence. The clinical spectrum of a rising PSA is wary wide and could comprehend patients with persistent or recurrent disease in the prostate or prostate bed, local lymph node recurrence or local and systemic disease. Given this spectrum an accurate methods of determining the clinical risk represented by a rising PSA value are critical to developing rational treatment strategies. The introduction of circulating tumor cells in clinical practice is still far, although they are considered as a sign of disease widespread, and therefore could be useful to assess the presence of systemic disease even if a local recurrence alone is suspected. Digital rectal exploration (DRE) and trans-rectal ultrasonography (TRUS) are considered the first clinical and diagnostic approach to identify the local recurrence of PCa, but are associated with a low detection rate and low diagnostic accuracies.

The combination of novel imaging modalities, such as magnetic resonance imaging (MRI) and radiolabeled choline positron emission tomography (PET/CT) able to identify the site of early local and distant recurrence may improve the capability of physicians to predict the clinical outcome and to propose appropriate therapies. In the present review we will discuss both clinical and diagnostic instrumentations, actually available in clinical practice, able to early identify the presence of recurrent PCa and to differentiate between local and distant relapse of tumor.

Early "biochemical" recurrence of disease

PSA

There is no single uniform definition for "biochemical relapse". The general idea is that patient who has undergone a radical prostatectomy (RP) should have no remaining normal, PSA-producing nonmalignant prostate tissue. In contrast, patients who have received any form of radiation therapy have an irradiated gland that will produce low levels of PSA by nonmalignant prostate epithelial cells. To date, both the American Urological Association and American Society of Radiation Oncology guidelines [3] and the European Association of Urology guidelines [4] recommend a definition of biochemical postprostatectomy recurrence as a detectable or rising PSA value >0.2 ng/mL with a second confirmatory level >0.2 ng/mL. After primary radiotherapy, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of >80%) is any PSA increase >2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir and the short-term hormonal manipulation.[5] It has to be noticed that the detection of a single abnormal PSA level does not necessarily indicate that a clinically significant event has occurred. As well, the presence of a rising PSA level alone does not necessarily imply that a patient will develop symptoms or die of his disease. Relapses after primary treatment of PCa occurs depended on initial tumor stages from 10% to 53%.[6] About 50% of pathological high risk patients (those with wide positive margins and/or pT3) and about 10% of those with low risk (negative margins and pT2) will develop a local relapse within 15 years from surgery.[7]

It has to be clarified that, in addition to the different primary tumor treatment, not all PSA assays have the same degree of sensitivity, so these could increase the variability of the PSA recurrence level. Mir *et al.* analyzed data from a single center with patients followed in the era of ultrasensitive PSA assays.[8] They compared 14 definitions of biochemical recurrence (BCR) after RP (6 standard BCR definitions and 8 alternative BCR definitions below currently accepted PSA thresholds [0.1 ng/mL]) and the risks of subsequent disease progression.[8] For patients with nomogram predicted 5-year progression free PSA<50% and 50-75%, a single PSA 0.05 ng/mL and two or more successive PSA rises 0.05 ng/mL may be reliable indicators of cancer recurrence. For patients at low risk of BCR, standard BCR definitions (PSA 0.2 ng/mL or 0.4 ng/mL and rising) should be used to identify men with recurrent PCa. This information is anticipated to be useful in identifying high risk patients who are appropriate candidates for early salvage radiotherapy with the potential for improved oncologic outcomes.

Monitoring PSA over time (or kinetic measurements) can aid information about the recurrence of disease. PSA velocity (PSAvel) and PSA doubling time (PSAdt) at the time of recurrence should be

entered into prediction models (or "nomograms") to aid patient counseling. For example, patients with elevated risk of developing metastases are those with a PSAdt<3 months, time to biochemical progression <3 years, biopsy Gleason Score (GS) 8-10 and clinical stage cT3b-T4.[9] Conversely, patients with a post treatment PSAdt more than 15 months, a time to biochemical progression more than 3 years, a pretreatment GS<7, or pretreatment clinical stage < cT3a were at significantly lower risk of clinical progression following biochemical failure.[9-11] Moreover, age, length of androgen deprivation, and even the type of the medication used will impact on the rate of biochemical failure.[12] Biochemical relapse occurs far earlier than the development of radiographically evident findings or findings on physical examination or biopsy. Understanding the behavior of PCa progression, combined with novel imaging modalities able to identify the site of early recurrence may eventually improve the capability of physicians to predict the clinical outcome and to propose appropriate therapies.

Circulating tumor cells

Early dissemination of cancer cells regardless of stage, grade, or tumor volume has been previously reported;[13] dissemination first occurs to the neurovascular structures and then onto the circulation. The process of metastatic spread from the primary tumor site to distant organs is still not well understood. Recent studies suggest an early spread of tumor cells to lymph nodes or bone marrow (BM) referred to as "disseminated tumor cells" or as "circulating tumor cells" (CTCs) when present in the peripheral blood.[14-16]With the development of new and reliable tools for CTC detection, CTC were detected in venous blood of locally to advanced cancer disease.[17, 18] In metastatic PCa, CTC numbers detected using CellSearch platform (an assay that enriches CTCs immunomagnetically with anti-EpCAM antibody conjugated to ferrofluids) are associated with overall survival (OS) and progression free survival (PFS). De Bono and colleagues found that CTC count was superior to PSA in predicting OS.[19, 20] Although in the last years, a lot of studies have been published reporting controversial results in PCa.[19] In 2013, Thalgott *et al.*[21] published a detailed systematic analysis of CTC according to different PCa stages. The Authors analyzed 20 patients with locally advanced PCa with no evidence of metastasis but at high risk of progression, 40 patients with mCRPCa, 15 patients with metastatic taxane refractory disease (mTRPCa) and 15 healthy donors. They did not find any statistically significant differences for CTC counts between patients with localized PCa and controls. Instead, a tendency of increase in the count was identified in mTRPCa as compared to mCRPCa patients, although it did not result statistically significant. In 2014, Jasmin Loh and colleagues enrolled 36 patients with high risk PCa.[22] They performed CTCs counting using CellSearch platform prior to any therapy. Only 5 patients showed CTCs but no correlation with outcome was found. In 2015, Pal *et al.*[23] analyzed 35 patients with high-risk localized PCa; for each patient they analyzed 4 blood draws: 2 weeks before RP, immediately before RP, 1 and 3 months after RP. They enumerated and characterized CTC with additional markers, such as CD133 for identifying CTC with stem cell-like characteristics and E-cadherin to examine epithelial to mesenchymal transition (EMT). EMT phenomena occurs in the earlier stages of disease and correlates with high GS and disease progression after RP, suggesting a relation between EMT phenotype and a more aggressive clinical behavior.[24, 25] To date, the small number of published reports, often devoted to investigate small pilot groups of patients entail that few conclusion can be reached about the association of CTC, and CTCs fragments in localized PCa; such as can be released for breast cancer where was analyzed a large cohort of patients with early breast cancer.[26] Many efforts are required to determine a consensus of CTCs phenotype and their predictive or prognostic value in PCa patients.

Early "radiological" recurrence of disease

Transrectal ultrasound + biopsy

Digital rectal examination is a subjective examination that cannot readily differentiate between malignant and benign tissues, although considering important for the clinical evaluation of the patients with suspicious for local recurrence of PCa. Transrectal ultrasound adds the ability to measure objectively and to document tumor size location, which can be helpful in the follow up of future treatment response or progression of the disease. In addition, ultrasound biopsy can be performed more accurately. Therefore, TRUS can be used in addiction to

DRE in the documentation of local recurrence.[27] In patients treated by RP, an asymmetric thickening or fullness of the anastomosis, loss of the integrity of the retro-anastomotic flat plane and/or the presence of hypoechoic lesion in the perianastomotic region are more often synonymous of local recurrence of disease. Kapoor *et al.*[28] reported that normal findings on postoperative TRUS do not exclude the possibility of local disease. However, the same group of authors suggested that any patients in whom there is a clinical suspicion of local disease after RP should undergo TRUS only to facilitate the localization of the urethrovesical junction and the prostatic fossa in order to direct systematic biopsies. These combined latter approaches (TRUS+biopsy) may make it possible to identify patients with disease that is amenable to local EBRT. In the majority of cases, local recurrence appears as a hypoechoic tissue or tissue thickening on ultrasound and is most likely to present at the level of anastomosis (60%).[29] However, the rate of positivity for TRUS and biopsy are related to the value of PSA, as reported by some authors.[30-34] In Table I is resumed available data from literature, about the detection rate of TRUS with or without biopsy according to PSA levels and other tumor characteristics. As illustrated, a lot of studies reported that in a wide range of PSA, the detection rate of TRUS associated with biopsy in almost of reports, for evaluating the presence of local recurrence of PCa ranging between 29% and 95%. Only in the study by Parra *et al.*[27] were reported data about the size of recurrence, while the site of disease were identified by Connolly *et al.*,[29] Leventis *et al.*[32] and Scattoni *et al.*[33] In accordance with this latter data, perianastomotic region and retrovesical space were the most frequent regions where the recurrence of disease can be detected by TRUS. However, Martino *et al.*[35] stated that TRUS provide a substantial advantage compared with DRE in the PCa recurrence localized at the bladder neck, since these lesions may be more difficult to be palpable because of the anterior location or because of merging of the lesion within the bladder wall. In Figure 1 is illustrated the local site of recurrences in PCa.

As reported by the studies from Leventis *et al.*[32] and Scattoni *et al.*,[33] the sensitivity, specificity, positive and negative predictive values for TRUS were higher in patients with a PSA level >2 ng/mL as compared those with a PSA<2 ng/mL. The sensitivity ranges between 80-100% and 69%, respectively in patients with PSA>2 ng/mL *vs.* <2 ng/mL (Table II). On the contrary, Deliveliotis *et al.*[36] reported a higher sensitivity and specificity for lower levels of PSA, probably due to the different characteristics of

TABLE I.—*Characteristics of collected studies about transrectal ultrasonography.*

Author, *ref*	Year of pub	N. of pts	US pattern	PSA level* (ng/mL)	Detection rate	Size of recurrence (mm)	Site or recurrence, (detection rate %)
Parra *et al.*,[27]	1990	20	Hypoechoic (70%) Isoechoic (30%)	28.6-31	19/20 (95%)	25-70	NA
Kapoor *et al.*,[28]	1993	15	-	0.3-26.9	8/15 (53%)**	NA	NA
Connolly *et al.*,[29]	1996	114	Hypoechoic (90%) Isoechoic (10%)	5.7 (0.2-35)	61/114 (54%)**	NA	Anastomosis (66%) Bladder neck (16%) Retrovesical space (13%) NV (5%)
Saleem *et al.*,[30]	1998	91	NA	7.8±13 (+) 5.4±13 (-)	50/91 (55%)**	NA	NA
Shekarriz *et al.*,[31]	1999	45	Hypoechoic (100%)	5.2±5.4	34/45 (76%)**	NA	NA
Leventis *et al.*,[32]	2001	99	Hypoechoic (100%)	2.4	41/99 (41%)**	NA	Anastomosis (61%) Bladder neck (54%) Retrovesical space (100%) Combinations (71%)
Scattoni *et al.*,[33]	2003	119	Hypoechoic (73%)	0.89 (0.2-28.8) 1.8±3.7	64/119 (54%)**	NA	Anastomosis (67%) Bladder neck (37%) Retrovesical space (94%)
Naya *et al.*,[34]	2005	100	NA	2 (0-3.4) (+) 0.7 (0-1) (-)	29/100 (29%)**	NA	NA
Deliveliotis *et al.*,[36]	2007	30	Hypoechoic	2.74±2	12/30 (40%)**	NA	NA

US: ultrasonography; *median (range) or mean±standard deviation; **with biopsy; NA: not available; NV: not visualized; (+) positive scan; (-) negative scan

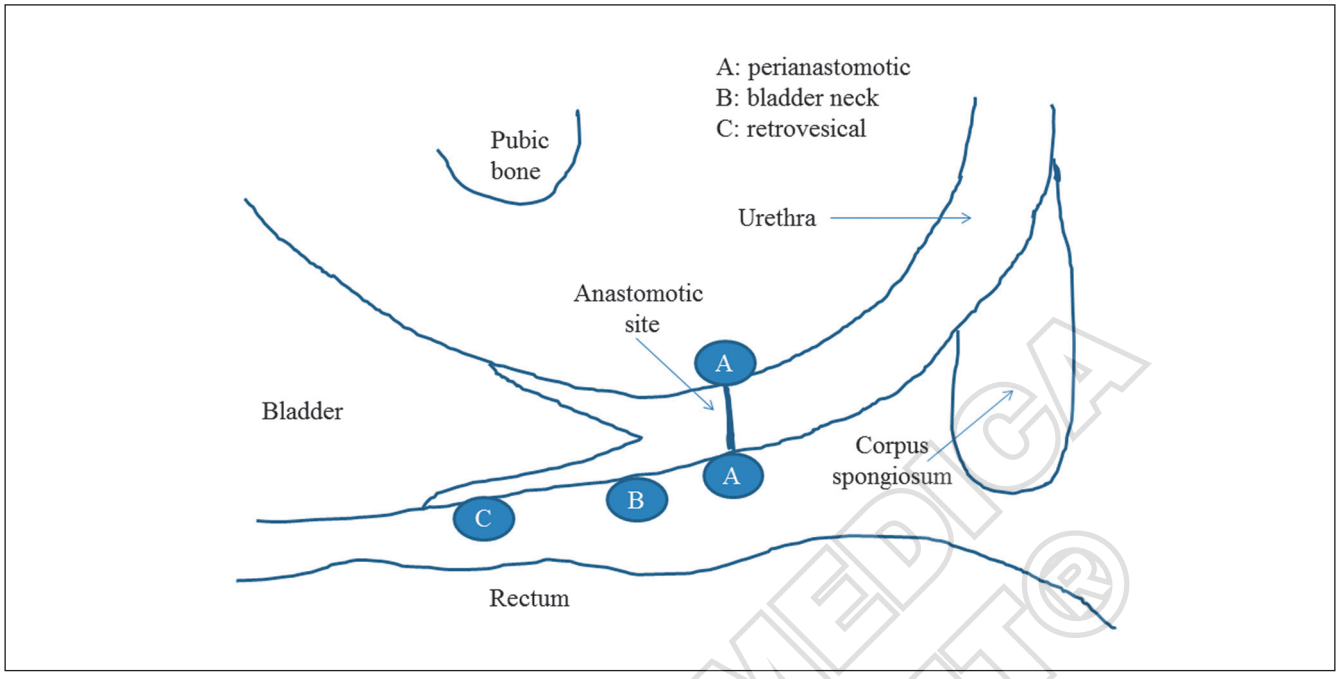

Figure 1.—Representation of the sites of local recurrence of prostate cancer.

TABLE II.—*Diagnostic accuracy of trans-rectal ultrasonography for the detection of local recurrence from prostate cancer.*

Authors, *ref.*		PSA<2 ng/mL	PSA>2 ng/mL
Leventis *et al.*,[32]	Sensitivity	69%	80%
	Specificity	74%	57%
	PPV	55%	67%
	NPV	84%	72%
Scattoni *et al.*,[33]	Sensitivity	69%	100%
	Specificity	63%	83%
	PPV	76%	85%
	NPV	64%	100%
Deliveliotis *et al.*,[36]	Sensitivity	100%	67%
	Specificity	90%	75%
	PPV	75%	75%
	NPV	100%	67%

PPV: positive predictive value; NPV: negative predictive value.

study population. Shekarriz *et al.*[31] have reported that higher is the PSA level higher is the likelihood to have a positive TRUS. Moreover, pathological stage, status of margins and original tumor size can influence the positivity of biopsy guided by TRUS, such as happens for PSA. Scattoni *et al.*[33] suggested to extent TRUS even to those patients with low serum PSA level since more than 70% of patients having a positive TRUS and a PSA<0.5 ng/mL had a biopsy proven local recurrence. Moreover, the authors suggested proceeding with a TRUS and multiple TRUS biopsies as soon as the PSA level rises above 0.2 ng/mL due to the fact that the advantage of an early diagnosis has been proven. Different opinion was released by Naya *et al.*[34] that suggested avoiding prostatic fossae biopsies in men with normal DRE and/or TRUS findings when the PSA level is less than 0.5 ng/mL because of the low rate of positivity.

MRI

MRI has a better diagnostic yield than TRUS and allows an evaluation of pelvic lymphnodes and bone status with the detection of all sites of PCa pelvic relapse in a single examination. The association of dynamic contrast-enhancement to MRI let to identify the site of recurrence: vesico-ureteral anastomosis in 52% of cases, retro-vesical space in 20%, and bladder neck in 16% and circumferential areas in 12%.[37] MRI after RP is a very useful tool to discriminate between loco-regional relapse and small amount of residual glandular health tissue, scar/fibrosis, and granulation tissue and it may even be able to assess the aggressiveness of nodule recurrence by means of apparent diffusion coefficient (ADC) values. The main advantage of MRI after RP and before to plan salvage radiotherapy is that multiparametric-MRI (mp-MRI) allows for an individualized field of irradiation, thereby maximizing toxicity to normal surrounding tissues. In this setting, mp-MRI findings could be used to apply a stereotactic boost to the recurrence site, potentially improving in this way the control of local disease and avoiding further loco-regional relapses over time.[38] Moreover, at present MRI is widely considered to be the state of art in detecting and localizing PCa recurrence in patients with biochemical relapse after definitive radiotherapy. In Table III are reported the diagnostic accuracies of some studies performing by MRI in patients with a biochemical recurrence of disease after RP and after radiotherapy. As illustrated, the sensitivity of TW2-MRI for the detection of local PCa recurrence ranges between 48-100%, with an intermediate value for low PSA levels (<1 ng/mL).[43] Conversely, after EBRT, MRI showed a wide range of sensitivities independently from the PSA values.

In most studies a 1.5-T MRI was used, and only in study by Roy *et al.*,[43] Kim *et al.*,[50] and Donati *et al.*[54] a 3-T MRI was employed. The main limitation of the listed studies was the gold standard reference. In fact, TRUS-guided sextant biopsy shows limited performances in the detection of cancer recurrence especially after EBRT, thus requiring repeated biopsies to reach final diagnosis,[55, 56] as aforementioned discussed. In addition to false-negative results due to sampling error, false-positive results may also occur, because the presence of malignant cells in biopsy specimen may represent biologically inactive tumor remnants, especially in the first 1-2 years after RT.[56] Paparo *et al.*[57] reported some information about the opportunity to combine MRI and TRUS. Their combination by various software-based coregistration platforms can improve the diagnostic yield of prostate biopsy in primary and recurrent PCa, thus reducing the number of false-negative results.

Different MRI protocols can improve the detection of PCa recurrence. Cirillo *et al.*[42] showed that dynamic contrast-enhanced (DCE) improves the di-

TABLE III.—*Diagnostic accuracies of TW2-MRI for the detection of local recurrence of prostate cancer.*

	Authors, *ref*	Year of pub, N of pts	PSA levels (ng/mL)	Study design	Gold standard	Sensitivity*	Specificity*	Accuracy*
After RP	Silverman *et al.*[39]	1997, 41	1.4**	Prospective	TRUS biopsy	100%	100%	-
	Sella *et al.*[40]	2004, 48	2.18:**	Retrospective	TRUS biopsy and PSA	95%	100%	-
	Casciani *et al.*[41]	2008, 46	1.9**	Retrospective	TRUS biopsy and PSA	48%	52%	48%
	Cirillo *et al.*[42]	2009, 72	1.51**	Retrospective	TRUS biopsy and PSA	61.4%	82.1%	69.4%
	Roy *et al.*[43]	2013, 28	0.98**	Retrospective	TRUS biopsy	56%	-	-
After RT	Rouviere *et al.*[44]	2004, 22	6.36**	Prospective	TRUS biopsy	26-44%	64-86%	54-60%
	Pucar *et al.*[45]	2005, 9	3.7**	Prospective	Histology	68%	96%	-
	Sala *et al.*[46]	2006, 45	3.57**	Prospective	Histology	36-76%	65-81%	-
	Haider *et al.*[47]	2008, 33	2.1**	Prospective	TRUS biopsy	38%	80%	74%
	Kim *et al.*[48]	2009, 36	3.44**	Prospective	TRUS biopsy	25%	92%	-
	Westphalen *et al.*[49]	2009, 59	NA	Retrospective	TRUS biopsy	62-74%	64-68%	63-71%
	Kim *et al.*[50]	2010, 24	2.76**	Retrospective	TRUS biopsy	27%	80%	67%
	Tamada *et al.*[51]	2011, 16	7.42**	Retrospective	TRUS biopsy	27%	99%	87%
	Kara *et al.*[52]	2011, 20	NA	Retrospective	TRUS biopsy	86.7%	100%	90%
	Akin *et al.*[53]	2011, 24	1.63**	Retrospective	TRUS biopsy	13-81%	25-88%	-
	Donati *et al.*[54]	2013, 53	NA	Retrospective	TRUS biopsy	54-66%	39-61%	-
	Roy *et al.*[43]	2013, 32	3.6**	Retrospective	TRUS biopsy	74%	-	-

RP: radical prostatectomy; RT: radiotherapy; TRUS: trans-rectal ultrasonography; NA: not available; *the diagnostic accuracy was evaluated for the T2WI; **mean value.

agnostic performance in detecting local PCa recurrence after RP as compared to unenhanced imaging. The authors enrolled 72 patients with a PSA levels ranging between 0.2-8.8 ng/mL demonstrating that the sensitivity and the specificity of DCE MRI and enhanced MRI, for lesion of 0.8-3.5 cm in size, were 84.1% *vs.* 61.4% and 89.3% *vs.* 82.1%, respectively. Moreover, in the same setting of patients, Sciarra *et al.*[58] and Panebianco *et al.*[59] found that the combination of magnetic resonance spectroscopy imaging (MRSI) and DCE allows higher diagnostic accuracy in identification of local recurrence of PCa. However, although these promising results, contrast enhancement advantages can be reduced by the concomitant administration of androgen deprivation therapy and the role of spectroscopy after RP is limited due to the artifacts of surgical clips and the unstandardized interpretation of the findings.[58, 60]

In patients with biochemical failure after EBRT, diffusion-weighted imaging (DWI) MRI or DCE MRI may be considered as a useful functional technique to detect and localize PCa recurrence, particularly for determining a target area for focal salvage therapy.[54, 61] However, DCE-MRI can helpful in patients with seed placement after brachytherapy (BRT), as DWI is prone to susceptibility artifacts and distortion in these cases.[38]

PET/CT

Early detection implies the identification of recurrent PCa at very low PSA values. As reported in the first section, the biochemical recurrence (BR) of disease should be suspected in different ways if patients have been treated by RP, by EBRT, or BRT as a primary treatment. In the majority of the available literature, PET/CT with radiolabeled Choline has shown a high detection rate in patients with a PSA level >2.0 ng/mL, and as suggested by Picchio *et al.*, and it is more accurate if performed in cases with a PSA>1.0 ng/mL.[62] However, some data are now available that consider the role of choline PET/CT in patients with very low detectable PSA level (<1.0 ng/mL). This it would be at a time in disease progression when patients would have greater benefit from salvage treatments, such as salvage RT, salvage lymph node dissection, or salvage RP. The main advantage of PET/CT with radiolabeled choline is the ability to detect the presence of distant recurrence of disease, thus changing the patient management (from local therapies to systemic treatments and vice versa). Nevertheless, PET/CT can miss micrometastatic disease, either in lymphnodes or in the bones. As reported by Schiavina *et al.*,[63] micrometastases in the bones are already present in about 30% of cases at the time of the primary treatment (Batson hypothesis and the "fertile soil" hypothesis), particularly in advanced stage of disease. As abovementioned, the evaluation of CTCs would be useful to assess the possibility of widespread disease in the blood borne disease. Nowadays, no data about the association between CTCs and results of radiolabeled Choline PET/CT in PCa patients are available. The presence of micrometastases at the time point of PET/CT could explain persistence or progression of disease despite radiation treatment according to the 11C-choline PET/CT results.[64] However, detecting extrapelvic relapses in the early phase of BR after RP or local therapies (BRT and EBRT) is still a major issue for clinicians. On the basis of tumor and node status, GS, PSA values, PSA kinetics and time to biochemical relapse, many risk tables and predictive nomograms have been generated to help clinicians in the detection of the site of recurrence (local *vs.* distant site).[65]

From an analysis of available literature, emerged that early salvage RT could be the best approach when a PSA failure is the initial finding (*i.e.* <0.5 ng/mL) and when anastomotic biopsy and diagnostic tools are not conclusive.[66-68] Other imaging modalities have been proposed, nevertheless, in a postoperative setting a lot of criticisms and uncertainties regarding the reliability and accuracy of MRI for prostatic bed relapse definition remain, although the inclusion of specific protocols would be useful. Reske *et al.*[69] evaluated the role of 11C-choline PET/CT scanning in 33 patients with biopsy-proven low-volume local recurrence after RP and found that in 30% of them, 11C-choline PET/CT failed to detect local recurrence. Souvatzoglou *et al.* found that just 7 (19%) of 37 patients who were referred for salvage RT to the prostatic fossa after RP because of PSA failure (PSA range; 0.3-1.8 ng/mL) showed 11C-choline uptake in the prostate bed by PET/CT.[64] Vees *et al.* compared endorectal coil MRI and 18F-choline PET/CT for detection of local recurrence in 11 patients with very low PSA levels at relapse (PSA level <0.8 ng/mL) after RP, and concluded that the sensitivity of 18F-Choline PET/CT was inferior to that of endorectal coil MRI (60% *vs.* 89%).[70]

However, from 2007 to date, more than 10 studies about the role of 18F/11C-choline PET/CT in

guided salvage lymph node dissection have been published.[71-78] The results are sometimes controversial, although in the majority of cases, PET/CT was able to detect the presence of tumor foci in pelvic and extrapelvic lymphnodes with high sensitivity (ranging between 85% and 100%) and moderate-high positive predictive value (ranging between 56% and 100%). Furthermore, as reported in the paper by Martini *et al.*,[75] Rigatti *et al.*,[76] Rinnab *et al.*,[77] and Winter *et al.*[78] the median value of PSA at the time of salvage treatment was less than 2.00 ng/mL (ranging between 1.5 and 1.85 ng/mL).

In a paper from von Eyben *et al.*,[79] they reported that 11C-choline and 18F-choline PET/CT are useful for the first imaging examination in patients with PCa and BR with PSA levels between 1.0 and 50 ng/mL. Moreover, in a "suggested" algorithm, the Authors reported that in case of PSA<1.0 ng/mL, active surveillance should be taken into consideration while PET/CT would be useful only if the value of PSA increases (>1.0 ng/mL). However, by analyzing in detail available literature (Table IV), we can found that 211 out of 844 patients (25%) with a PSA level <1.0 ng/mL with an 11C/18F-choline PET/CT had a positive scan.[80-87] Therefore to avoid the lack of positive findings in patients with very low detectable PSA levels, some predictive models or appropriate criteria could be used. As an example, the addition of PSA kinetic variables, GS and staging at initial disease would be useful, but probably not enough. The addition of PSA kinetics, such as PSAdt and PSAvel for the prediction of a positive PET/CT scan has already been assessed by Marzola *et al.*,[80] Castellucci *et al.*[84, 88] and Giovacchini *et al.*[89] In particular, a PSAdt<3 months and a PSAvel>0.75 ng/mL/year are associated with a positive PET/CT finding. Moreover, as recently reported by Cimitan *et al.*,[79] 47% of patients with a GS>7 at initial diagnosis (on the surgical specimen or biopsy) and a PSA level <1 ng/mL showed a positive PET/CT scan. The detection rate of PET/CT tends to increase with the level of PSA. As reported in Table V, the detection rate ranges between 59% and 100% in patients with a median PSA of 1.5-2 ng/mL. As previously reported, the choice of salvage treatments depends on the presence of extrapelvic disease. From the analysis of published articles, we found that the detection rate of PET/CT in extrapelvic site was ranged between 15.4% and 88%, in patients with a PSA level <5 ng/mL. This result can help urologists and oncologists in decision making for treatment of PCa patients. In fact, as illustrated in Table V, choline PET/CT has an important effect on the patients' management and especially for those with low PSA levels. In particular, in many cases a change in RT planning was seen (N.=55/642; 8.6%) [64, 84] or addiction of salvage RT (N.=7/34; 21%).[70, 72] However, in the majority of patients, radiolabeled choline PET/CT was able to switch from salvage to systemic treatments (N.=36/283; 30%) or from systemic to salvage ones (N.=47/211; 22.3%).

In Figures 2, 3 are reported some examples of positive 18F-Choline PET/CT scans in patients with local and distant recurrence of disease, at different PSA levels.

Anti-3-18F-fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC) is an investigational radiopharmaceutical agent, recently introduced. Its uptake is related to the functional activity of 2 different amino acid transporters (amino acid system of alanine, serine and cysteine, and independent "L" large-neutral amino acid transport system). A few papers are now available about the clinical application of ^{18}F-FACBC PET/CT in PCa. As recently reported by

TABLE IV.—*Detection rates of radiolabelled PET/CT for PSA level <1.0 ng/mL.*

Author, Ref.	Year of pub	N. pts	Radiolabelled choline	Type of treatment		Detection rate
				RP	RT	
Krause *et al.*[85]	2008	22	11C	NA	NA	8 (36%)
Giovacchini *et al.*[82]	2010	141	11C	141	-	27 (19%)
Mamede *et al.*[81]	2012	71	11C	71	-	7 (9.9%)
Schillaci *et al.*[83]	2012	10	18F	10		2 (20%)
Marzola *et al.*[80]	2013	64	18F	64		19 (29.7%)
Mitchell *et al.*[86]	2013	34	11C	NA	NA	15 (44.1%)
Castellucci *et al.*[84]	2014	291	11C	291		67 (23%)
Cimitan *et al.**, [87]	2015	211	18F	138	19	66 (31.3%)

RP: radical prostatectomy; RT: radiotherapy; NA: not available for patients with PSA<1 ng/mL;
*residual patients: hormone therapy alone (N.=14) and not available (N.=40).

TABLE V.—*Characteristics and content of studies involving radiolabeled Choline PET/CT.*

Authors, ref.	Year-pub.	N pts	Median PSA* ng/mL	Radioisotope	Detection rate			Change in management
					Total	Pelvic	Extrapelvic	
Heinisch *et al.*[99]	2006	17	0-5	18F	7 (41%)	2 (29%)	5 (71%)	-
Vees *et al.*[70]	2007	11	0.35 (0.11–0.73)	18F	5 (45%)	5 (100%)	-	1 (1%) salvage external beam radiotherapy
Scattoni *et al.*[100]	2007	21	1.98 (0.23–23.12)	11C	21 (100%)	21 (100%)	-	-
Krause *et al.*[85]	2008	37	0-3	11C	16 (43%)	-	-	-
Reske *et al.*[69]	2008	36	2 (0.3-12.1)	11C	24 (67%)	-	-	31 (94%)
Giovacchini *et al.*[82]	2010	289	0.2-5	11C	104 (36%)	-	-	-
Breewsma *et al.*[101]	2010	16	0-4	11C	13 (81.3%)	11 (84.6%)	2 (15.4%)	-
Winter *et al.*[102]	2010	6	2.04 (0.67-4.51)	11C	6 (100%)	6 (100%)	-	6 (100%)
Lépinoy *et al.*[103]	2011	31	3.8 (0.5-59.1)	18F	31 (100%)	17 (54.8%)**	10 (32.3%)** + 4 (12.9%) pelvic/extra	-
Wurshmidt *et al.*[104]	2011	26	1.9 (0.42-65)	18F	24 (93%)	6 (25%)	10 (42%) + 8 (33%) pelvic/extra	-
Souvatzoglou *et al.*[64]	2011	37	0.5 (2.5-12.3)	11C	11 (30%)	11 (100%)	-	5 (13%) change in RT planning
Castellucci *et al.*[105]	2011	104	0.93 (0.67-1.10)	11C	29 (28%)	7 (24%)	9 (31%, LN) + 13 (45%, Bone)	-
Rigatti *et al.*[106]	2011	72	1.5 (IQR: 0.8–5.17)	11C	72 (100%)	47 (65%)	25 (35%)	-
Jilg *et al.*[71]	2012	26	-	11C/18F	6 (23%)	6 (100%)	-	6 (23%) additional RT
Martini *et al.*[75]	2012	8	1.62 (0.17-2.93)	11C	8 (100%)	8 (100%)	-	-
Mamede *et al.*[81]	2012	71	<0.5	11C	7 (9.9%)	7 (100%)	-	-
Schillaci *et al.*[83]	2012	49	5.35±5.04 (mean±SD)	18F	33 (67%)	4 (12%)	29 (88%)	29 (59%) from localized to systemic
Soyka *et al.*[96]	2012	156	3.40	18F	124 (79%)	63 (51%)	61 (49%)	33 (21%) from palliative to salvage 15 (10%) from curative to palliative 8 (5%) switch curative 2 (1%) switch palliative 17 (11%) adaptive therapy
Marzola *et al.*[80]	2013	64	<0.5	18F	19 (29%)	1 (5%)	15 (79%) + 3 (16%) pelvic/extra	-
Mitchell *et al.*[86]	2013	115	0-5	11C	78 (67.8%)	-	-	-
Castellucci *et al.*[84]	2014	605	1 (0.2-2.0)	11C	172 (28.4%)	83 (48%)	55 (32%) + 17 (10%) pelvic/extra	50 (8%) change in RT planning
Ceci *et al.*[97]	2014	150	3.7 (0.1-66)	11C	109 (72.7%)	64 (42.7%)	31 (20.7%) + 14 (9.3%) pelvic/extra	13/95 (14%) from salvage to systemic 14/55 (25%) from systemic to salvage 10/41 (24%) no treatments
Alongi *et al.*[98]	2014	32	1.9 (0.27-64)	11C	19 (59%)	13 (68%)	4 (21%) + 2 (11%) pelvic/extra	8 (26%) from local to systemic treatments (ADT and Chemo)
Alongi *et al.*[107]	2014	15	4.59 (0.18-64.2)	11C	15 (100%)	15 (100%)	-	-
Winter *et al.*[78]	2015	13	1.64 (0.5-9.55)	11C/18F	13 (100%)	13 (100%)	-	-
Cimitan *et al.*[87]	2015	364	0-2	18F	128 (35%)	42 (33%)	86 (67%)	-

*before PET/CT; Pelvic was define as choline uptake in prostatic fossae/gland and in pelvic lymph nodes; Extrapelvic was defined as choline uptake in extrapelvic lymph nodes or in skeletal/visceral sites **inside or outside the clinical target volume defined by Radiation Therapy Oncology Group (CTV_{RTOG}); RT: radiotherapy; ADT: androgen deprivation therapy; IQR: interquartile range; SD: standard deviation

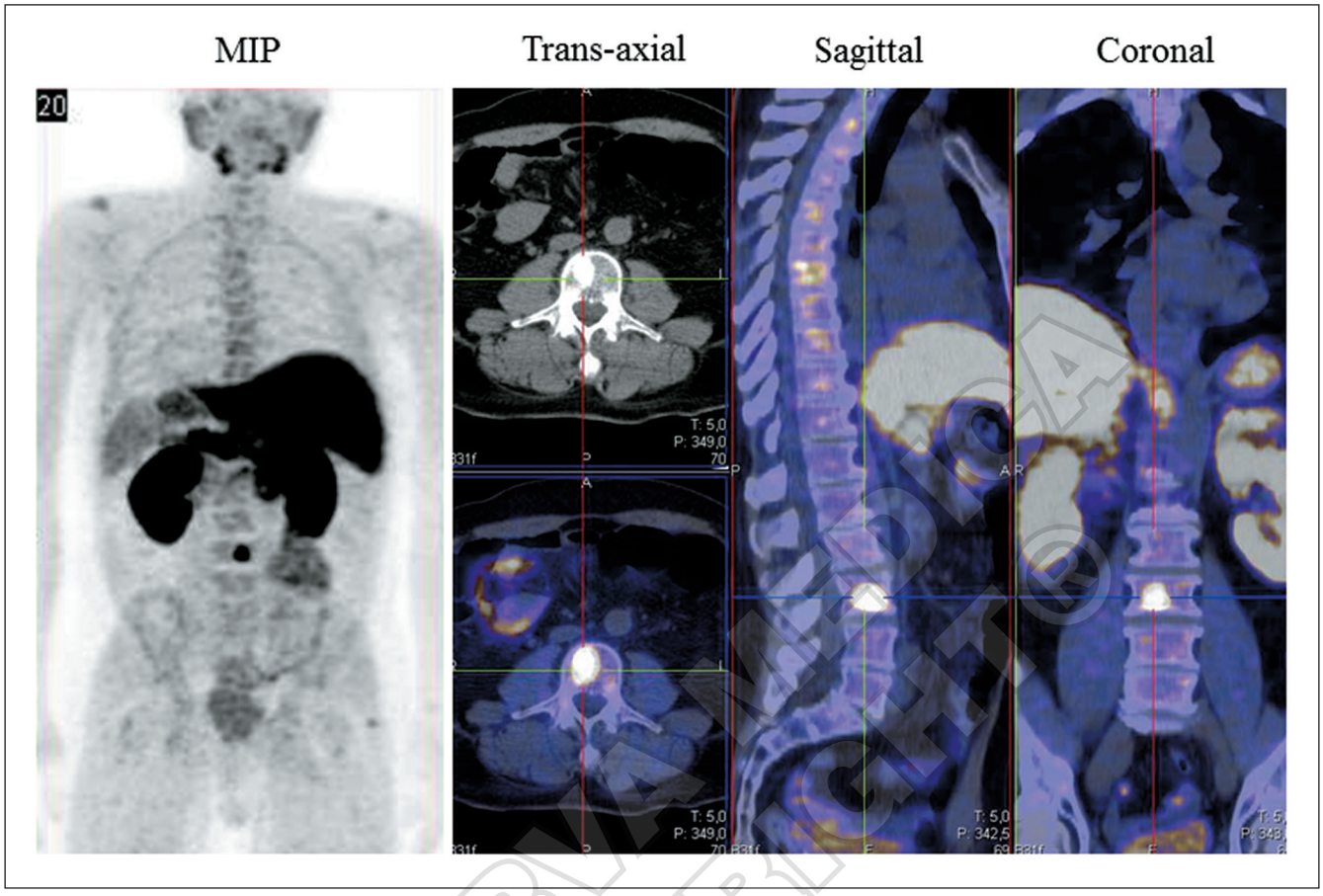

Figure 2.—A 64-year old man with a prostate cancer (radical prostatectomy in 2008). Increase in PSA level during therapy with LH-RH analogues (0.35 ng/mL in September 2011, 0.62 ng/mL in December 2011 and 1.52 ng/mL in March 2012). In 23rd March 2012,18F-Choline PET/CT showed a focal uptake in the lumbar vertebra corresponding to a osteoblastic lesion at CT-images.

Nanni [90, 91] and by Savir-Barich *et al.*,[92] the detection rate of this radiopharmaceutical agent is higher than 11C-Choline PET/CT. Similar results have also been seen with a new agent, ^{86}Ga-prostate specific membrane antigen (PSMA). It is a specific membrane antigen overexpressed in PCa cells. It was able to provide higher signal to background images than ^{18}F-choline PET/CT in one study, therefore

TABLE VI.—*Detection rates of new radiopharmaceutical agents for low PSA levels.*

Author, Ref.	Year of pub	N pts	PSA level (ng/mL)	Radiopharmaceutical agent	Choline PET/CT	Detection rate	
						Other RFA	Choline
Savir-Baruch *et al.*[92]	2011	5	Range: 1.1-20.5	^{18}F-FACBC	-	80%	-
Nanni *et al.*[90]	2013	15	2.1±2.0	^{18}F-FACBC	11C-choline	40%	20%
Nanni *et al.*[91]	2014	28	Median: 2.9	^{18}F-FACBC	11C-choline	61.1%	39%
Afshar-Oromich *et al.*[108]	2012	37	≤2.82	^{68}Ga-PSMA	18F-choline	68.8%	43.8%
Afshar-Oromich *et al.**, [93]	2014	20	2.62 (0.51-73.60)	^{68}Ga-PSMA	-	80%	-
Elber *et al.*[109]	2015	248	0.2-0.5	^{68}Ga-PSMA	-	57.9%	-
			0.5-1			72.7%	
Afshar-Oromich *et al.*[110]	2015	319	≤1.0	^{68}Ga-PSMA	-	53%	-

RFA: radiopharmaceutical agent; *PET/MRI.

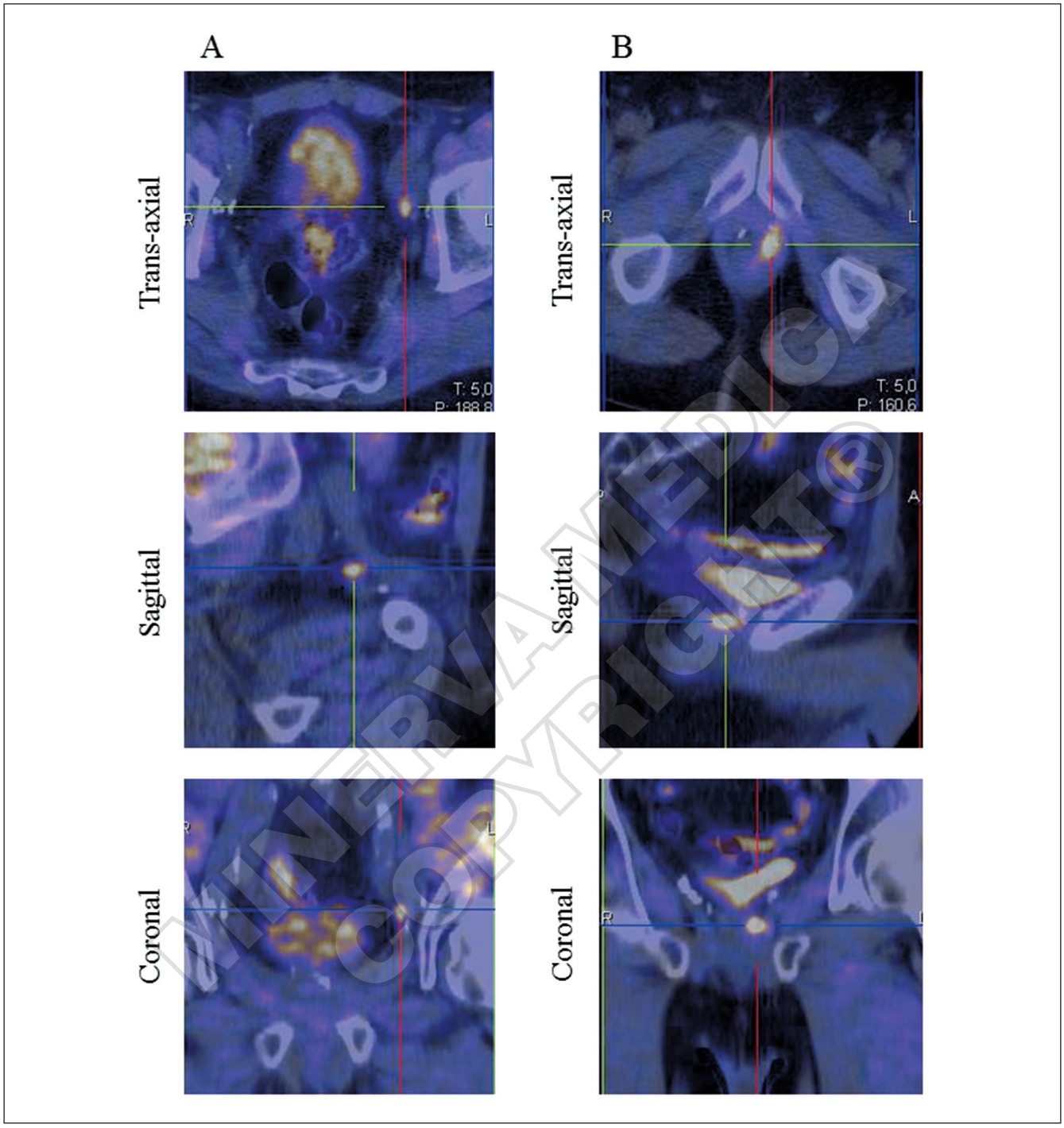

Figure 3.—A) 75-year old man with a prostate cancer (radical prostatectomy in 2008) who showed an increase of PSA levels (0.27 ng/mL in October 2014 and 0.54 ng/mL in February 2015). PET/CT with 18F-Choline PET/CT performed at the end of February 2015 showed a focal uptake in left internal iliac lymph node (size: 0.8 mm). B) A 65-year old man with a slight increase in PSA after 6 months from radical prostatectomy (March 2012). The patient was send to 18F-Choline PET/CT in December 2012 that detected the presence of local prostatic fossae recurrence with a PSA level=0.82 ng/mL.

contributing to a significantly improved detection rate even for low PSA levels.[93] Some recent studies have demonstrated the advantages, both in lymph node and bone metastasis detection with ^{68}Ga PSMA as compared to radiolabeled choline PET/CT. Table VI reports the detection rates for ^{18}F-FACBC and ^{68}Ga-PSMA for low PSA levels. As clearly illustrated, also for low PSA values, ^{68}Ga PSMA and ^{18}F-FACBC are superior to choline PET/CT (the detection rate ranges between 40-80%), although a direct comparison with biopsy or histology has not been performed. Recently, the introduction of hybrid PET/MRI systems has demonstrated some advantages in term of resolution imaging, especially for the detection of recurrence in prostatic bed.[94] However, Choline PET/MRI and PET/CT have similar sensitivity in terms of qualitative analysis, but from the study by Wetter *et al*.[95] emerged some information that the SUV_{max} and SUV_{mean} in PCa and in bone metastases were lower for PET/MRI than PET/CT scan. These differences can be explained by 1) different attenuation correction and 2) different acquisition times for comparative studies (images after 3 hours and 20 minutes/bed *vs.* after 1 hour and 2 minutes/bed, respectively PET/MRI and PET/CT). Although encouraging, the results derived from new tracers and PET/MRI should be still considered under evaluation and therefore as experimental tools. Larger comparative and randomized trials are required for their definitive introduction in clinical practice.

Conclusions

Currently, we can suppose a specific role for each of the above mentioned clinical and imaging examination:

1. PSA serum values and PSA kinetics (like PSAdt and PSAvel) should be considered as "alarm signs" of disease recurrence and therefore used as early biochemical markers for indicating the presence of a viable PCa cells, in patients already treated by RP or EBRT;

2. CTCs can be considered as a marker of systemic or widespread disease, although their relationship with treatment management and prognosis of PCa patients remains indeterminate;

3. DRE, TRUS and biopsy remain a common choice in patients with biochemical recurrence of PCa, but their role in the management of these patients need to be further addressed, in particular by comparing them with new imaging modalities, such as MRI and PET/CT;

4. mp-MRI after RP is indicated to diagnose small local cancer recurrence in a range of PSA serum values between 0.2 and 1 ng/mL. In addition an MRI based RT approach treating the prostatic fossa with a boost to local recurrence improves the treatment therapeutic ratio and allows a decrease of locoregional relapses;

5. choline PET/CT is the most promising whole body imaging modality in detecting distant metastases of PCa, because of its ability to depict small pathological lymph nodes and bone metastases with a high sensitivity, specificity, and accuracy;

6. the recent development of hybrid PET/MRI scanners could improve the diagnostic accuracy in depicting local PCa relapses in post-prostatectomy fossa. Moreover, the inclusion of new radiopharmaceutical agents in clinical practice would improve the diagnostic accuracy of PET/CT also for low PSA levels (*i.e.* < 0.50 ng/mL).

References

1. Ferlay J, Shin HR, Bray F *et al*. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer. Int J Cancer 2010;127:2893-917.
2. Stamey TA, Yang N, Hay AR *et al*. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987;317:909-16.
3. Thompson IM, Valicenti RK, Albertsen P *et al*.. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol 2013;190:441-9.
4. Mottet N, Bellmunt J, Briers E *et al*. EAU Guidelines on Prostate Cancer. Eur Urology 2015 [Epub ahead of print].
5. Roach M 3rd, Schellhammer P, Shipley WU *et al*. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965-74.
6. Han M, Partin AW, Zahurak M *et al*. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol 2003;169:517-523.
7. Pfitzenmaier J, Pahernik S, Tremmel T *et al*. Positive surgical margins after radical prostatectomy: do they have an impact on biochemical or clinical progression? BJU Int 2008;102:1413-8.
8. Mir MC, Kattan MW, Klein EA *et al*. Optimal definition of biochemical recurrence after radical prostatectomy depends on pathologic risk factors: identifying candidates for early salvage therapy. Eur Urol 2014;66:204-10.
9. Zumsteg ZS, Spratt DE, Romesser PB *et al*. The Natural History and Predictors of Outcome Following Biochemical Relapse in the Dose Escalation Era for Prostate Cancer Patients Undergoing Definitive External Beam Radiotherapy. Eur Urol 2015;67:1009-16.
10. D'Amico AV, Moul J, Carroll PR *et al*. Prostate specific antigen doubling time as a surrogate end point for prostate cancer specific mortality following radical prostatectomy or radiation therapy. J Urol 2004;172:S42-7.

11. Denham JW, Steigler A, Wilcox C *et al.* Time to biochemical failure and prostate-specific antigen doubling time as surrogates for prostate cancer-specific mortality: evidence from the TROG 96.01 randomised controlled trial. Lancet Oncol 2008;9:1058-68.
12. Lukka H, Warde P, Pickles T *et al.* Controversies in prostate cancer radiotherapy: consensus development. Can J Urol 2001;8:1314-22.
13. Moreno JG, Croce CM, Fischer R *et al.* Detection of hematogenous micro-metastasis in patients with prostate cancer. Cancer Res 1992;52:6110-2.
14. Kruck S, Gakis G, Stenzl A. Circulating and disseminated tumor cells in the management of advanced prostate cancer. Adv Urol 2012;2012:135281.
15. Pantel K, Brakenhoff RH. Dissecting the metastatic cascade. Nat Rev Cancer 2004;4:448-56.
16. Hüsemann Y, Geigl JB, Schubert F *et al.* Systemic spread is an early step in breast cancer. Cancer Cell 2008;13:58-68.
17. Allard WJ, Matera J, Miller MC *et al.* Tumor cells circulate in the peripheral blood of all major carcinomas but not in healthy subjects or patients with nonmalignant diseases. Clin Cancer Res 2004;10:6897-904.
18. Nagrath S, Sequist LV, Maheswaran S *et al.* Isolation of rare circulating tumour cells in cancer patients by microchip technology. Nature 2007;450:1235-9.
19. Danila DC, Heller G, Gignac GA *et al.* Circulating tumour cell number and prognosis in progressive castration-resistant prostate cancer. Clin Cancer Res 2007;13:7053-8.
20. de Bono JS, Scher HI, Montgomery RB *et al.* Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res 2008;14:6302-9.
21. Thalgott M, Rack B, Maurer T *et al.* Detection of circulating tumor cells in different stages of prostate cancer. J Cancer Res Clin Oncol 2013;139:755-63.
22. Loh J, Jovanovic L, Lehman M *et al.* Circulating tumor cell detection in high-risk non-metastatic prostate cancer. J Cancer Res Clin Oncol 2014;140:2157-62.
23. Pal SK, He M, Wilson T *et al.* Detection and phenotyping of circulating tumor cells in high-risk localized prostate cancer. Clin Genitourin Cancer 2015;13:130-6.
24. Contreras HR, Ledezma RA, Vergara J *et al.* The expression of syndecan-1 and -2 is associated with Gleason score and epithelial-mesenchymal transition markers, E-cadherin and beta-catenin, in prostate cancer. Urol Oncol 2010;28:534-40.
25. Gravdal K, Halvorsen OJ, Haukaas SA *et al.* A switch from E-cadherin to N-cadherin expression indicates epithelial to mesenchymal transition and is of strong and independent importance for the progress of prostate cancer. Clin Cancer Res 2007;13:7003-11.
26. Lucci A, Hall CS, Lodhi AK *et al.* Circulating tumor cells in non-metastatic breast cancer:a prospective study. Lancet Oncol 2012;13:688-95.
27. Parra RO, Wolf RM, Huben RP. The use of transrectal ultrasound in the detection and evaluation of local pelvic recurrence after a radical pelvic operation. J Urol 1990;144:707-9.
28. Kapoor DA, Wasserman NF, Zhang G *et al.* Value of transrectal ultrasound identifying local after radical prostatectomy. Urology 1993;41:594-7.
29. Connolly JA, Shinohara K, Presti Jr. JC *et al.* Local recurrence after radical prostatectomy: characteristics in size, location, and relationship to prostate-specific antigen and surgical margins. Urology 1996;47:225-30.
30. Saleem MD, Sanders H, El Naser MA *et al.* Factors predicting cancer detection in biopsy of the prostatic fossa after radical prostatectomy. Urology 1998;51:283-6.
31. Shekarriz B, Upadhyay J, Wood DP *et al.* Vesicouretheral anastomosis biopsy after radical prostatectomy: predicitive value of prostate specific antigen and pathologic stage. Urology 1999;54:1044-8.
32. Leventis AK, Shariat SF, Slawin KM. Local recurrence after radical prostatectomy: correlation of US features with prostatic fossa biopsy findings. Radiology 2001;219:432-9.
33. Scattoni V, Roscigno M, Raber M *et al.* Multiple vesico-uretheral biopsies following radical prostatectomy: the predicitive roles of TRUS, DRE, PSA and the pathological stage. Eur Urol 2003;44:407-14.
34. Naya Y, Okihara K, Evans RB *et al.* Efficacy of prostatic fossa biopsy in detecting local recurrence after radical prostatectomy. Urology 2005;60:350-5.
35. Martino P, Scattoni V, Galosi AB *et al.* Role of imaging ansd biopsy to assess local recurrence after definitive treatment for prostate carcinoma (surgery, radiotherapy, criotherapy, HIFU). World J Urol 2011;29:595-605.
36. Deliveliotis C, Manousakas T, Chrisofos M *et al.* Diagnostic efficacy of transrectal ultrasound-guided biopsy of the prostatic fossa in patients with rising PSA following radical prostatectomy. World Urol 2007;25:309-13.
37. Martino P, Scattoni V, Galosi AB *et al.* Role of imaging and biopsy to assess local recurrence after definitive treatment for prostate carcinoma (surgery, radiotherapy, cryotherapy, HIFU). World J Urol 2011;29:595-605.
38. Barchetti F, Panebianco V. Multiparametric MRI for recurrent prostate cancer post radical prostatectomy and post-irradiation therapy. Biomed Res Int 2014;2014:316272.
39. Silverman JM, Krebs TL. MR imaging evaluation with a transrectal surface coil of local recurrence of prostatic cancer in men who have undergone radical prostatectomy. Am J Roentgenol 1997;168:379-85.
40. Sella T, Schwartz LH, Swindle PW *et al.* Suspected local recurrence after radical prostatectomy: endorectal coil MR imaging. Radiology 2004;231:379-85.
41. Casciani E, Polettini E, Carmenini E *et al.* Endorectal and dynamic contrast-enhanced MRI for detection of local recurrence after radical prostatectomy. Am J Roentgenol 2008;190:1187-92.
42. Cirillo S, Petracchini M, Scotti L *et al.* Endorectal magnetic resonance imaging at 1.5 Tesla to assess local recurrence following radical prostatectomy using T2-weighted and contrast-enhanced imaging. Eur Radiol 2009;19:761-9.
43. Roy C, Foudi F, Charton J *et al.* Comparative sensitivities of functional MRI sequences in detection of local recurrence of prostate carcinoma after radical prostatectomy or external-beam radiotherapy. Am J Roentgenol 2013;200:W361-W368.
44. Rouvière O, Valette O, Grivolat S *et al.* Recurrent prostate cancer after external beam radiotherapy: value of contrast-enhanced dynamic MRI in localizing intraprostatic tumor—correlation with biopsy findings. Urology 2004;63:922-7.
45. Pucar D, Shukla-Dave A, Hricak H *et al.*. Prostate cancer: correlation of MR imaging and MR spectroscopy with pathologic findings after radiation therapy—initial experience. Radiology 2005;236:545-53.
46. Sala E, Eberhardt SC, Akin O *et al.*. Endorectal MR imaging before salvage prostatectomy: tumor localization and staging. Radiology 2006;238:176-83.
47. Haider MA, Chung P, Sweet J *et al.* Dynamic contrast-enhanced magnetic resonance imaging for localization of recurrent prostate cancer after external beam radiotherapy. Int J Radiat Oncol Biol Phys 2008;70:425-430.
48. Kim CK, Park BK, Lee HM. Prediction of locally recurrent prostate cancer after radiation therapy: incremental value of 3T diffusion-weighted MRI. J Magn Reson Imaging 2009;29:391-7.
49. Westphalen AC, Kurhanewicz J, Cunha RMG *et al.* T2-weighted endorectal magnetic resonance imaging of prostate cancer after external beam radiation therapy. Int Braz J Urol 2009;35:171-80.
50. Kim CK, Park BK, Park W *et al.* Prostate MR imaging at 3T using a phasedarrayed coil in predicting locally recurrent prostate cancer after radiation therapy: preliminary experience. Abdominal Imaging 2010;35:246-52.
51. Tamada T, Sone T, Jo Y *et al.* Locally recurrent prostate cancer after high-dose-rate brachytherapy: the value of diffusion-weight-

ed imaging, dynamic contrast-enhanced MRI and T2-weighted imaging in localizing tumors. Am J Roentgenol 2011;197:408-14.
52. Kara T, Akata D, Akyol F *et al*. The value of dynamic contrast-enhanced MRI in the detection of recurrent prostate cancer after external beam radiotherapy: correlation with transrectal ultrasound and pathological findings. Diagn Interv Radiol 2011;17:38-43.
53. Akin O, Gultekin DH, Vargas HA *et al*. Incremental value of diffusion weighted and dynamic contrast enhanced MRI in the detection of locally recurrent prostate cancer after radiation treatment: preliminary results. Eur Radiol 2011;21:1970-8.
54. Donati OF, Jung SI, Vargas HA *et al*. Multiparametric prostate MR imaging with T2-weighted, diffusion-weighted, and dynamic contrast-enhanced sequences: are all pulse sequences necessary to detect locally recurrent prostate cancer after radiation therapy? Radiology 2013;268:440-50.
55. D'Amico AV, Crook J, Beard CJ *et al*. Radiation therapy for prostate cancer. In:Walsh PC, Retik AB, editors. Campbell's Urology. 8th edition. Philadelphia, PA, USA: WB Saunders; 2002. p. 3147-70.
56. Crook J, Malone S, Perry G *et al*. Postradiotherapy prostate biopsies: what do they really mean? Results for 498 patients. Int J Radiat Oncol Biol Phys 2000;48:355-67.
57. Paparo F, Piccardo A, Bacigalupo L, Romagnoli A, Piccazzo R, Monticone M, *et al*.. Value of bimodal 18F-Choline-PET/MRI and trimodal 18F-choline-PET/MRI/TRUS for the assessment of prostate cancer recurrence after radiation therapy and radical prostatectomy. Abdom Imaging 2015; in press
58. Sciarra A, Panebianco V, Salciccia S *et al*. Role of dynamic contrast-enhanced magnetic resonance (MR) imaging and proton MR spectroscopic imaging in the detection of local recurrence after radical prostatectomy for prostate cancer. Eur Urol 2008;54589-600.
59. Panebianco V, Sciarra A, Lisi D *et al*. Prostate cancer:1HMRS-DCEMR at 3T versus [(18)F]choline PET/CT in the detection of local prostate cancer recurrence in men with biochemical progression after radical retropubic prostatectomy (RRP). Eur J Radiol 2012;81:700-8.
60. Wu LM, Xu JR, Gu HY *et al*. Role of magnetic resonance imaging in the detection of local prostate cancer recurrence after external beam radiotherapy and radical prostatectomy. Clin Oncol 2013;25:252-64.
61. Panebianco V, Barchetti F, Sciarra A *et al*. Prostate cancer recurrence after radical prostatectomy: the role of 3-T diffusion imaging in multi-parametric magnetic resonance imaging. Eur Radiol 2013;23:1745-52.
62. Picchio M, Briganti A, Fanti S *et al*. The role of choline positron emission tomography/computed tomography in the management of patients with prostate-specific antigen progression after radical treatment of prostate cancer. EurUrol 2011;59:51-60.
63. Schiavina R, Ceci F, Borghesi M *et al*. The dilemma of localizing disease relapse after radical treatment for prostate cancer: which is the value of the actual imaging techniques? Curr Radiopharm 2013;6:92-5.
64. Souvatzoglou M, Krause BJ, Purschel A *et al*. Influence of 11C-choline PET/CT on the treatment planning for salvage radiation therapy in patients with biochemical recurrence of prostate cancer. Radiother Oncol 2011;99:193-200.
65. Katz MS, Zelefsky MJ, Venkatraman ES *et al*. Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. J Clin Oncol 2003;21:483-9.
66. Stephenson AJ, Scardino PT, Kattan MW *et al*. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007;25:2035-41.
67. Koppie TM, Grossfeld GD, Nudell DM *et al*. Is anastomotic biopsy necessary before radiotherapy after radical prostatectomy? J Urol 2001;166:111-5.
68. Stephenson AJ, Shariat SF, Zelefsky MJ *et al*. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA 2004;291:1325-32.
69. Reske SN, Blumstein NM, Glatting G. [11C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy. Eur J Nucl Med Mol Imaging 2008;35:9-17.
70. Vees H, Buchegger F, Albrecht S *et al*. 18F-choline and/or 11C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy. BJU Int 2007;99:1415-20.
71. Jilg CA, Leifert A, Schnell D *et al*. Toxicity and quality of life after choline-PET/CT directed salvage lymph node dissection and adjuvant radiotherapy in nodal recurrent prostate cancer. Radiation Oncology 2014;9:178.
72. Jilg CA, Rischke HC, Reske SN *et al*. Salvage Lymph Node Dissection with Adjuvant Radiotherapy for Nodal Recurrence of Prostate Cancer. J Urol 2012;188:2190-7.
73. Passoni NM, Suardi N, Abdollah F *et al*. Utility of [11C]choline PET/CT in guiding lesion targeted salvage therapies in patients with prostate cancer recurrence localized to a single lymph node at imaging: results from a pathologically validated series. Seminars and Original Investigations 2014;32:9-16.
74. Karnes RJ, Murphy CR, Bergstralh EJ *et al*. Salvage lymph node dissection for prostate cancer nodal recurrence detected by 11c-choline positron emission tomography/computerized tomography. J Urol 2015;193:111-6.
75. Martini T, Mayr R, Trenti E *et al*. The role of 11C-choline-PET/CT-guided secondary lymphadenectomy in patients with PSA failure after radical prostatectomy: lessons learned from eight cases. Advances in Urology 2012;1-4
76. Rigatti P, Suardi N, Briganti A *et al*. Pelvic/retroperitoneal salvage lymph node dissection for patients treated with radical prostatectomy with biochemical recurrence and nodal recurrence detected by [11C]choline positron emission tomography/computed tomographY. Eur Urol 2011;60:935-43.
77. Rinnab L, Mottaghy FM, Simon J *et al*. [11 C]choline PET/CT for targeted salvage lymph node dissection in patients with biochemical recurrence after primary curative therapy for prostate cancer. Urol Int 2008;81:191-7.
78. Winter A, Henke R-P, Wawrosche K. Targeted salvage lymphadenectomy in patients treated with radical prostatectomy with biochemical recurrence: complete biochemical response without adjuvant therapy in patients with low volume lymph node recurrence over a long-term follow-up. BMC Urology 2015;15:10-8.
79. von Eyben FE, Kairemo K. Meta-analysis of (11)C-choline and (18)F-choline PET/CT for management of patients with prostate cancer. Nucl Med Commun 2014;35:221-30.
80. Marzola MC, Chondrogiannis S, Ferretti A *et al*. Role of 18F-choline PET/CT in biochemically relapsed prostate cancer after radical prostatectomy: correlation with trigger PSA, PSA velocity, PSA doubling time, and metastatic distribution. Clin Nucl Med 2013;38:e26-32.
81. Mamede M, Ceci F, Castellucci P *et al*. The role of 11C-choline PET imaging in the early detection of recurrence in surgically treated prostate cancer patients with very low PSA level <0.5 ng/mL. Clin Nucl Med 2013;38:e342-5.
82. Giovacchini G, Picchio M, Coradeschi E *et al*. Predictive factors of [(11)C]choline PET/CT in patients with biochemical failure after radical prostatectomy. Eur J Nucl Med Mol Imaging 2010;37:301-9.
83. Schillaci O, Calabria F, Tavolozza M *et al*. Influence of PSA, PSA velocity and PSA doubling time on contrast-enhanced 18F-choline PET/CT detection rate in patients with rising PSA after radical prostatectomy. Eur J Nucl Med Mol Imaging 2012;39:589-96.
84. Castellucci P, Ceci F, Graziani T *et al*. Early biochemical relapse after radical prostatectomy: which prostate cancer patients may benefit from a restaging 11C-Choline PET/CT scan before salvage radiation therapy? J Nucl Med 2014;55:1424-9.

85. Krause BJ, Souvatzoglou M, Tuncel M *et al*. The detection rate of [11C]choline-PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. Eur J Nucl Med Mol Imaging 2008;35:18-23.
86. Mitchell CR, Lowe VJ, Rangel LJ *et al*. Operational characteristics of (11)c-choline positron emission tomography/computerized tomography for prostate cancer with biochemical recurrence after initial treatment. J Urol 2013;189:1308-13.
87. Cimitan M, Evangelista L, Hodolič M *et al*. Gleason score at diagnosis predicts the rate of detection of 18F-choline PET/CT performed when biochemical evidence indicates recurrence of prostate cancer: experience with 1,000 patients. J Nucl Med 2015;56:209-15.
88. Castellucci P, Fuccio C, Nanni C *et al*. Influence of trigger PSA and PSA kinetics on 11C-Choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. J Nucl Med 2009;50:1394-400.
89. Giovacchini G, Picchio M, Parra RG *et al*. Prostate-specific antigen velocity versus prostate-specific antigen doubling time for prediction of 11C choline PET/CT in prostate cancer patients with biochemical failure after radical prostatectomy. Clin Nucl Med. 2012;37:325-31.
90. Nanni C, Schiavina R, Boschi S *et al*. Comparison of 18F-FACBC and 11C-choline PET/CT in patients with radically treated prostate cancer and biochemical relapse: preliminary results. Eur J Nucl Med Mol Imaging 2013;40:S11-S17.
91. Nanni C, Schiavina R, Brunocilla E *et al*. 18F-FACBC compared with 11C-choline PET/CT in patients with biochemical relapse after radical prostatectomy:a prospective study in 28 patients. Clinical Genitourinary Cancer 2014;12:106-10.
92. Savir-Baruch B, Schuster DM, Jarkas N *et al*. Pilot Evaluation of Anti-1-amino-2-[18F]fluorocyclopentane-1- carboxylic acid (anti-2-[18F]fACPC) PET-CT in Recurrent Prostate Carcinoma. Mol Imaging Biol 2011;13:1272-7.
93. Afshar-Oromieh A, Zechmann CM, Malcher A *et al*. Comparison of PET imaging with a 68Ga-labelled PSMA ligand and 18F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2014;41:11-20.
94. Arce-Calisaya P, Souvatzoglou M, Eiber M *et al*. Sensitivity of PET/MRI to detect recurrence of prostate cancer. Eur J Nucl Med Mol Imaging 2013;40:799.
95. Wetter A, Lipponer C, Nensa F *et al*. Evaluation of the PET component of simultaneous [18F]choline PET/MRI in prostate cancer: comparison with [18F]choline PET/CT. Eur J Nucl Med Mol Imaging 2014;41:79-88.
96. Soyka JD, Muster MA, Schmid DT *et al*. Clinical impact of 18F-choline PET/CT in patients with recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2012;39:936-43.
97. Ceci F, Hermann K, Castellucci P *et al*. Impact of 11C-choline PET/CT on clinical decision making in recurrent prostate cancer: results from a retrospective two-centre trial. Eur J Nucl Med Mol Imaging 2014;41:2222-31.
98. Alongi F, Comito T, Villa E *et al*. What is the role of [11C]choline PET/CT in decision making strategy before post-operative salvage radiation therapy in prostate cancer patients? Acta Oncol 2014;1:990-2.
99. Heinisch M, Dirisamer A *et al*. Positron emission tomography/computed tomography with F-18-fluorocholine for restaging of prostate cancer patients: meaningful at PSA< 5 ng/ml? Mol Imaging Biol 2006;8:43-8.
100. Scattoni V, Picchio M, Suardi N *et al*. Detection of lymph-node metastases with integrated [11C]choline PET/CT in patients with PSA failure after radical retropubic prostatectomy: results confirmed by open pelvic-retroperitoneal lymphadenectomy. Eur Urol 2007;52:423-9.
101. Breeuwsma AJ, Prium J, van den Bergh ACM *et al*. Detection of local, regional, and distant recurrence in patients with PSA relapse after external-beam radiotherapy using 11c-choline positron emission tomography. Int J Radiation Oncology Biol Phys 2010;77:160-4.
102. Winter A, Uphoff J, Henke R-P *et al*. First results of [11C]choline PET/CT-guided secondary lymph node surgery in patients with PSA failure and single lymph node recurrence after radical retropubic prostatectomy. Urol Int 2010;84:418-23.
103. Lépinoy A, Cochet A, Cueff A *et al*. Pattern of occult nodal relapse diagnosed with 18F-fluoro-choline PET/CT in prostate cancer patients with biochemical failure after prostate-only radiotherapy. Radiother Oncol 2014;111:120-5.
104. Würschmidt F, Petersen C, Wahl A *et al*. [18F]fluoroethylcholine-PET/CT imaging for radiation treatment planning of recurrent and primary prostate cancer with dose escalation to PET/CT-positive lymph nodes. Radiat Oncol 2011;6:44.
105. Castellucci P, Fuccio C, Rubello D *et al*. Is there a role for 11C-choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase <1.5 ng/ml? Eur J Nucl Med Mol Imaging 2011;38:55-63.
106. Rigatti P, Suardi N, Briganti A *et al*. Pelvic/retroperitoneal salvage lymph node dissection for patients treated with radical prostatectomy with biochemical recurrence and nodal recurrence detected by [11c]choline positron emission tomography/computed tomography. Eur Urol 2011;60:935-43.
107. Alongi F, Liardo RLE, Iftode C *et al*. 11C choline PET guided salvage radiotherapy with volumetric modulation arc therapy and hypofractionation for recurrent prostate cancer after HIFU failure: preliminary results of tolerability and acute toxicity. Res Treat 2014;13:395-401.
108. Afshar-Oromieh A, Haberkorn U, Eder M *et al*. [68Ga]Gallium-labelled PSMA ligand as superior PET tracer for the diagnosis of prostate cancer: comparison with 18F-FECH. Eur J Nucl Med Mol Imaging 2012;39:1085-6.
109. Eiber M, Maurer T, Souvatzoglou M *et al*. Evaluation of Hybrid 68Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. J Nucl Med 2015;56:668-74.
110. Afshar-Oromieh A, Avtzi E, Giesel FL *et al*. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2015;42:197-209.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Epub ahead of print on July 24, 2015.